

Study of Preterm Infants with Different Gestational Age: Modifying Amikacin Sulphate Dosage Regimen

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(Received: June, 2017)

(Accepted: June, 2017)

ABSTRACT

The study was performed to determine the gestational age of preterm infants that requires amikacin therapeutic drug monitoring. A study was conducted in preterm infants on amikacin therapy with gestational age of 28 to 36 weeks. Therapeutic drug monitoring in preterm infants was performed based on their individual pharmacokinetics to avoid ototoxicity and nephrotoxicity. Its prerequisite, because of their immuno-compromised and challenging clinical conditions, to provide an effective and optimized dosage regimen. One compartment model was used to calculate pharmacokinetics and modulated amikacin dosage regimen based on obtained amikacin peak and trough concentration at 3rd dose.

Amikacin inadequate level, especially high trough found in 60 % patients were optimized for therapeutic level by tailoring dosage regimen. Correlation between percentage modification of dose and dosing time interval with percentage changes of amikacin peak and trough concentration at modulated dose was studied.

KEY WORDS: amikacin, dosing time interval, modulated dose, pharmacokinetic, preterm infants, therapeutic drug monitoring (TDM)

INTRODUCTION:

The crucial paradigm in preterm infants is their extensive pharmacological variability due to rapidly evolving physiological developments^[1]. Preterm infants are prone to severe infections due to their immature and immuno-compromised health conditions^[2]. The differential body composition and renal immaturity among preterm infants contributes to enlarge pharmacokinetics inter-individual variability^[3]. In preterm infants, around 75% of body weight is comprised of extracellular fluid that leads to direct impact on the amikacin volume of distribution because of its high water-soluble property^[4].

Amikacin sulphate belongs to aminoglycosides (AG) family, approved by the United State

Food & Drug Administration (USFDA) and it requires therapeutic drug monitoring (TDM) due to its narrow therapeutic index and overt toxicity from 2 to 10 %^[5,6]. Amikacin is considered as the mainstay in the antimicrobial therapy for systemic bacterial infections due to its bactericidal and efficacious action^[3,7,8].

Amikacin therapy in preterm infants is of major concern due to nephrotoxicity, ototoxicity, developmental differences during this period and frequent changes in renal clearance^[9]. The drug accumulation which leads to drug toxicity is directly proportional to excretion of the drug. Due to the narrow therapeutic index of amikacin, it necessitates careful monitoring of blood drug concentration to avoid sub-therapeutic and toxic pharmacological effects^[7,10,11].

The scenario of amikacin pharmacokinetics in the preterm infants is complex^[1,12]. Amikacin is mainly eliminated by the kidney, and preterm infants have lower elimination rates due to their immature kidney function which results in prolonged half-life compared to mature infants^[13,14]. Total body clearance in preterm infants is lower as it is associated with the gestational age and birth weight. Clearance and half-life are influenced by the developmental stage of

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preterm infants and are considered as one of the main parameters in tailoring dosage regimen^[14,15].

Low elimination of amikacin is inversely proportional to half-life and results in prolonged time duration, which results in higher amikacin serum trough concentration^[16,17]. Serum creatinine clearance is widely used as key parameter available to observe the renal system function. Usually physicians use creatinine clearance value and modify dosage regimen. However, creatinine clearance is not accurate to measure dosage regimen (modified dose and dosing time interval) of amikacin sulphate. In our study, we had observed preterm infants with normal serum creatinine having high amikacin trough concentration than expected.

TDM in preterm infants is internationally recommended to evaluate efficacy and potential toxicity^[5,15]. TDM minimizes toxicity and medical intervention based on a customized dosage regimen. This improves the quality of drug utilization, safety, efficacy and cost effectiveness in clinical studies^[15,18].

It exemplifies the therapeutic dosage and develops evidence based treatment plans that relies on specific pharmacokinetic parameter of the individual patient^[9].

The paucity of data with regard to amikacin pharmacokinetics study in preterm infants necessitates to establish a precise amikacin dosage regimen to avoid inconsistent serum concentration fluctuation^[16]. This study is designed on evidence based therapeutic dosage regimen for preterm infants based on individual pharmacokinetic parameter.

In our study, we observed preterm infants of different gestational age (ascending weeks of gestational age) with different serum creatinine clearance. We distinguished the range of preterm infants gestational age requiring therapeutic drug monitoring.

MATERIALS AND METHODS:

This study was conducted at Dr Prabhakar Kore Basic Science Research Center in collaboration with the Neonatal Intensive Care Unit at Karnataka Lingayat Education, Dr Prabhakar Kore Hospital & Medical Research Center, India during year 2015. The ethical approval was obtained from human ethical committee of the Karnataka Lingayat Education University. Informed consent was obtained from the parents of the enrolled pre-term infants in the study. The patients included in the study were preterm infants and selection of subjects was performed based on the clinical condition and assessment by the expert

neonatologist. The sample size of preterm infants enrolled in the study is five. The inclusion criteria of preterm infants was gestational age between 28 to 36 weeks, on intravenous amikacin therapy and with no congenital abnormalities. Exclusion criteria were not fulfilling the inclusion criteria, and preterm infants whose parents denied permission to enroll their infants in the study.

Demographic data such as gestational age and weight of the preterm infants enrolled in the study were collected (Table 1).

Amikacin was administered as an intravenous infusion over 0.5 hr (hours) using a syringe driver. Preterm infants amikacin dosage regimen, was calculated based on their current body weight, using standard recommended dose of 7.5 mg/kg every 12 hours for preterm infants born or less than 7 days old.

As per reported studies and data, amikacin attains a steady state kinetics before the third dose administration. Amikacin samples were collected by heel prick using a sterile lancet and from an indwelling arterial catheter. From each preterm infant, 0.5 mL of blood was collected for amikacin peak and trough level monitoring before and after modification of dosage regimen. Blood samples were collected 60 min post-IV infusion of third dose amikacin and 30 min prior to the fourth dose. A similar sample collection practice was followed after administering the modulated sixth dosage of amikacin that was calculated based on the pharmacokinetic parameters of individual patient.

Amikacin concentration analysis in serum was carried out using ultra high performance liquid chromatography (UPLC) with fluorescence detector (Shimadzu) at Dr. Prabhakar Kore Basic Science Research Center, Karnataka, India^[19].

PHARMACOKINETICS STUDY:

The least-squares linear regression analysis of concentration-time data was integral to illustrate the one compartment model. Amikacin pharmacokinetics parameter data analysis was found to fit one compartment model^[3].

The following equation was used to calculate pharmacokinetics with one compartment open model based on the Sawchuk-Zaske method:

$$[K_e = (\ln C_{pk} - C_{tr}) / \Delta t],$$

where, K_e = elimination rate constant (hr^{-1}),

C_{pk} = measured amikacin serum peak concentration (mg/L),

C_{tr} = measured amikacin serum trough concentration (mg/L), Δt = time interval between C_{pk} and C_{tr}

Table 1: Demographic and 3rd dose of Amikacin obtained peak and trough concentration data in preterm infants.

Preterm Infants Patients Parameters	Pateint 1	Pateint 2	Pateint 3	Pateint 4	Pateint 5
Born Gestational Age (weeks)	36	34	31	31	29
Birth Weight (kg)	1.33	2.37	1.1	1.32	0.7
Amikacin Dose Administered (mg)	10	17.2	8.2	10	5.7
Serum Creatinine (mg/dL)	0.74	0.76	1.12	1.07	0.71
Amikacin Highest Blood Conc. (mg/L) (Peak)*	17	21.83	26.2	23.4	25
Amikacin Lowest Blood Conc. (mg/L) (Trough)*	2.78	3.58	10.39	9.5	10
Time Interval between Sample Collection (hr)	10.25	10.05	10.4	10.5	10.05
Observed Amikacin Peak and Trough level*	Within optimum range	Within optimum range	High Trough level	High Trough level	High Trough level
Require Modulation of Amikacin Dosage Regimen	No	No	Yes	Yes	Yes

*Amikacin optimum therapeutic range of peak - 15 to 30 mg/L and trough - less than 5 mg/L.

$[t_{1/2} = 0.693 / K_e]$, where, $t_{1/2}$ = half-life (hr)
 $[V_d = [D/T (1 - e^{-K_e T})] / [K_d (C_{max} - (C_{min} e^{-K_d T}))]]$,
 where, V_d = volume of distribution (L/kg), D = dose administered (mg/kg), K_e = elimination rate constant (h^{-1}), T = duration of infusion (hr), C_{pk} = concentration in serum after 30 minutes at the end of infusion (mg/L), C_{tr} = concentration in serum 30 minutes before the administration of next dose (mg/L)
 $[CL = (K_d) (V_d)]$, where, CL = total body clearance (CL) (L/hr/kg).

In preterm infants, amikacin target concentration for peak is 15 – 30 mg/L and trough is less than 5 mg/L, for therapeutically effective treatment with minimized toxic effects.

Dose modulation recommended in patients whose amikacin peak and trough concentration were not found within the optimal therapeutic range. Such as, if amikacin peak concentration found above or below 15-30 mg/L or trough concentration were found above 5 mg/L. Due to the low elimination rate constant as it depends on the individual PK response based on amikacin dose administered with duration of dose interval.

The peak concentration in patients found below the range indicates that amikacin is not reaching its optimum level and patient will be deprived of getting therapeutic response and lead to treatment failure. The peak concentration in patients found above the optimum range leads to amikacin toxicity. High trough level due to low elimination rate leading

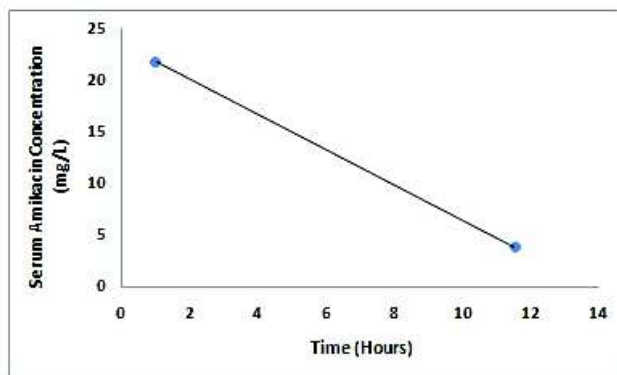


Figure 1: Amika cin serum concentration (mg/ L) in preterm infants at peak and trough sampling timing.

to accumulation in the body with routine dosage procedure also results in high peak concentration. In such cases, dose modulation is suggested either by an increase in the duration of dose interval or modification of the administered dose. In order to optimize the trough level, duration of dose interval was increased to decline the trough level along with an increase in dose to maintain the peak level since peak level attaining optimum level may result from high trough level.

Based on the results obtained from pharmacokinetic data, revised dosage regimen, was calculated by using the following formulas:

The recommended dosage interval was calculated using, $[t = (\ln(C_{max})) - (\ln(C_{min})) * V_d / CL]$, where, t = recommended dosing interval (hr), C_{pk}

Table 2: Amikacin peak and trough concentration at 3rd and 6th dose and calculated pharmacokinetic parameters. Based on 3rd dose obtained pharmacokinetic parameters (a) calculated modulated dose and (b) dosing interval.

Preterm Infants Patients Parameters	Patient 1		Patient 2		Patient 3		Patient 4		Patient 5	
	3rd	6th	3rd	6th	3rd	6th	3rd	6th	3rd	6th
Dose										
TDM initiated at Gestational Age (weeks + days)	36 + 4	36 + 6	34 + 5	34 + 7	31 + 4	31 + 6	31 + 5	31 + 7	29 + 2	29 + 4
Amikacin dose administered (mg)	10	10	17.2	17.2	8.2	9.9	10	13.7	5.7	7.2
Amikacin lowest blood conc. (mg/L) (Trough)*	2.78	2.53	3.58	4.08	10.39	2.9	9.5	3.5	10	4
Amikacin highest blood conc. (mg/L) (Peak)*	17	18.14	21.83	24.55	26.2	20.58	23.4	24.05	25	22
Time interval between sample collection (hr)	10.25	10.05	10.05	10.5	10.4	18.3	10.5	19.15	10.05	18.75
Elimination rate constant (Kd) (1/hr)	0.18	0.20	0.17	0.17	0.09	0.11	0.09	0.10	0.09	0.09
Half Life (t1/2) (hr)	3.92	3.54	4.02	4.05	7.79	6.47	8.07	6.89	7.60	7.62
Volume of Distribution (V _d) (L)	0.66	0.66	0.91	0.79	0.49	0.54	0.68	0.47	0.36	0.39
Total Body Clearance (CL) (L/hr)	0.12	0.13	0.16	0.13	0.04	0.06	0.06	0.05	0.03	0.03
# Based on Amikacin 3 rd dose the obtained peak and trough concentration calculated modulated dose and dosing time interval.										
Modulated Dosing Time interval**	-	-	-	-	20.14	-	20.87	-	19.65	-
Modulated Dose**	-	-	-	-	9.86	-	13.69	-	7.22	-

*Optimum therapeutic range of peak - 15 to 30 mg/L and trough - less than 5 mg/L.
 ** Amikacin targeted peak and trough concentration – 24 and 4 mg/L.

= maximum desired drug concentration (mg/L), C_{tr} = minimum desired drug concentration (mg/L), V_d = calculated volume of distribution (L/kg), CL = calculated total body clearance.

Recommended dosage was calculated as [Dose = [(C_{pk} - C_{tr}) * V]], where, V_d = calculated volume of distribution (L/kg), C_{pk} = maximum desired drug concentration (mg/L), C_{tr} = minimum desired drug concentration (mg/L).

Dose modification performed based on the selection of desired level of peak and trough value by obtaining total body clearance and volume of distribution. These PK parameters depend upon the elimination rate constant of drug and dose administered based on preterm infants gestational age and body weight.

RESULTS AND DISCUSSION:

A typical amikacin peak and trough concentration vs sampling timing curve was obtained from pharmacokinetic data (Figure 1). Based on the

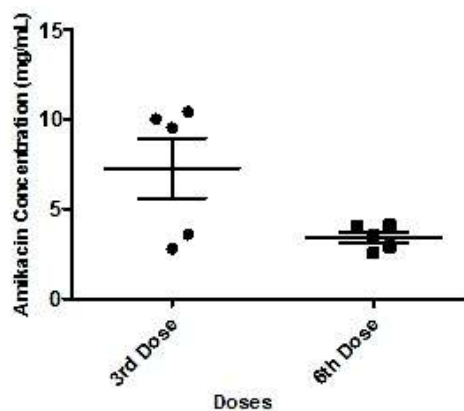


Figure 2: Amikacin trough concentration at 3rd dose and 6th dose.

developed PK model obtained PK parameter values based on 3rd dose in preterm infants required TDM (Table 2).

Different gestational age preterm infant patients had been studied:

Patient 1: Gestational age of the patient was 36 weeks. Based on the birth weight of the preterm infant patient

Table 3: Difference of modulated dose and dosing time interval from calculated dose and dosing time interval.

Patients Parameters	Pateint 3	Patient 4	Patient 5
Difference of Modulated dose from Calculated Dose (mg)	+1.7	+3.7	+1.5
Difference of Modulated Dosing Time Interval from Calculated Dosing Time Interval (hr)	+8.14	+8.87	+7.65
Percentage Modification of Dose from Calculated Dose (%)	20.73	37.00	26.32
Percentage Modification of Time Interval from 12 hr (%)	67.83	73.92	63.75

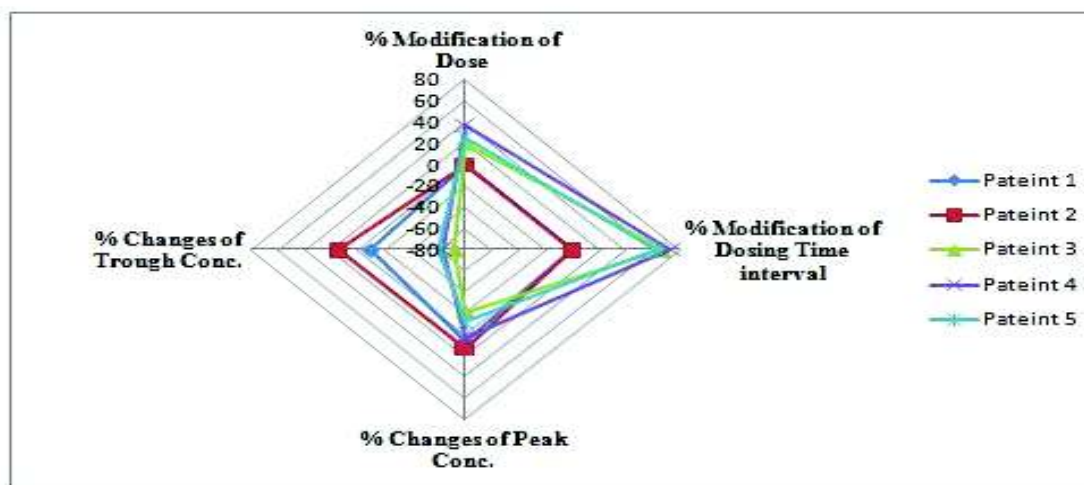


Figure 3: Represents the correlation between percentage modification of dose and dosing time interval with percentage changes of amikacin peak and trough concentrations in all preterm infants patients at 6th dose.

i.e. 1.33 kg, amikacin dose was administered as 10 mg/b.i.d.

Upon analysis of blood samples, amikacin peak and trough concentration were found within the optimum therapeutic range i.e. 17 and 2.8 mg/L respectively. Obtained results indicate that amikacin was evenly distributed in the patient and timely eliminated from the body (Table 2). In preterm infant of gestational age of 36 weeks, kidney system was developed. Serum creatinine was 0.74 mg/dL found within the optimum range^[20]. Amikacin same dosage regimen had been continued without dosage modulation.

Patient 2: Preterm infant of gestational age 34 weeks with birth weight of 2.37 kg, amikacin dose administered based on empirical method was 17.2 mg/b.i.d. Amikacin 3rd dose analyzed peak and trough samples, the results were 18.1 and 2.5 mg/L. It represents that amikacin was timely eliminating from the body system without accumulation.

Obtained volume of distribution and clearance values were as 0.66 L and 0.13 L/hr shows well functioning of the kidney. Serum creatinine was

0.76 mg/dL. Amikacin dose modulation not required as the obtained amikacin concentration was found within the optimum therapeutic range. Amongst all patients, this preterm infant obtained the highest volume of distribution and total body clearance values. This shows the kidney organ system was mature and amikacin well distributed and eliminated from the body system.

Patient 3: Preterm infant patient gestational age was 31 weeks with birth weight of 1.1 kg based on which amikacin 8.2 mg/b.i.d. was administered. Amikacin 3rd dose collected sample results show that amikacin trough concentration was found above the optimum therapeutic level (<5 mg/L) as 10.4 mg/L, although the peak concentration was found within the optimum range (15-30 mg/L) as 26.2 mg/L.

Amikacin half life was found high as 7.79 hr with lowest elimination rate constant as 0.09 1/hr. Amikacin low elimination rate extends its stay in body system for longer hours resulting in high half life which directly leads to high trough value in patient. Because of patient low total body clearance as being low (0.04 L/hr), dosing time interval needs to be

extended to reduce the trough level, with an increase in dose to maintain the peak level for 6th dose. Amikacin dosing time interval was extended from 12 hrs to 20 hours, to eliminate excess amikacin. However, dose concentration was increased from 8.2 mg to 9.9 mg to achieve therapeutic dose. In similar manner, amikacin 6th dose analyzed sample results were found to be 20.6 and 2.9 mg/L respectively. Trough concentration was found to be reduced to an optimum level and peak concentration was maintained within the optimum range.

Modification of dose and time interval from 3rd to 6th dose in patient was 1.7 mg and 8 hour from the calculated dose to modulated dose. And the percentage of dose modification was 20.73 % and percentage of modified dosing time interval was 67.83%. Percentage of target trough concentration to be obtained was 61.50 %. However, after modification of amikacin dosage regimen, the trough concentration was achieved by 72.09 %. It represents that patient renal function is under developing stage and response obtained after modification was 117 % (Table 3).

Patient 4: This preterm was infant born at gestational age of 31 weeks with birth weight of 1.32 kg. Based on his weight, amikacin dose administered was 10 mg/b.i.d. Collected peak and trough concentration blood samples at 3rd results were found to be 23.4 and 9.5 mg/L respectively. Amikacin trough level was obtained higher than the optimum level, whereas peak level was found within the optimum range. Continuation of same dosage will impact both peak and trough level in the body. Amikacin dosage regimen modulation is a requisite. Amikacin 6th dose modulated based on obtained PK parameter values from 10 mg to 13.7 mg with dosing time interval of 21 hr. Obtained peak and trough samples results were 24.1 and 3.5 mg/L respectively. Trough concentration was reduced by extending the dosing interval, and peak concentration was maintained by increasing the dosage amount.

Modification of dose and dosing time interval performed in this patient was 3.7 mg and 8.9 hour from calculated to modulated dose. Percentage of modified dose and dosing time interval observed in patient was 37.0 % and 73.92 %. Patient percentage of target trough concentration to be achieved was 57.89 % and accomplished was 67.37 %. Percentage of response observed in patient achieved optimum trough concentration after the modification was 116 % (Table 3).

Patient 5: This preterm infant patient was the youngest, 29 weeks lowest gestational age with the

birth weight of less than a kg i.e., 0.7 kg. Based on gestational age and birth weight the calculated amikacin dose administered to the patient was 5.7 mg/b.i.d.

Upon analysis of 3rd dose collected peak and trough level samples, the results were found to be 25.0 and 10.0 mg/L respectively. Calculated PK parameters results show that the elimination rate constant was low which resulted in increased half-life of amikacin as 7.6 hr. Compared to other 4 patient, Vd and Cl were found low. Due to age being have 29 weeks of gestational age, kidney system was in under developing stage.

Modulated amikacin 6th dose administered from calculated dose was 7.2 mg from 5.7 mg at 20 hr dosing time interval. Amikacin 6th dose obtained peak and trough analyzed sample results were 22.0 and 4.0 mg/L, respectively. Modulation of amikacin dosage regimen results in obtaining optimum therapeutic peak and trough concentration in preterm infant patient.

Percentage of response for optimum trough concentration was found 100 %. Percentage of dose and dosing time interval modified were 26.32 % and 63.75% from the calculated dose to modulated dose. The required decrease in trough concentration in patient to obtain an optimum level was 60% and achieved by modulated dosage regimen was 60%. It represents 100 % response obtained in this patient with therapeutically effective pharmacological response based on an optimized therapeutic range (Table 3).

Preterm infant patients with gestational age of 36 and 34 weeks have mature kidney system as amikacin blood peak and trough levels were found within the optimal therapeutic range. However, below this gestational age, renal system was under developmental stage as the low elimination rate was found constant in preterm infants. Higher trough levels were found due to high half life ($t_{1/2}$)(hr) of amikacin because of its time stay in the body due to low elimination rate constant^[21]. Elimination rate constant is directly proportional to total body clearance. Total body clearance was also found low in preterm infants among those under 32 weeks of gestational age^[22,23].

Peak concentration in all preterm infant patients was found within the optimum range. The difference in peak concentration at 3rd and 6th doses from the optimum range (15-30 mg/L) was observed (Table 4).

Variation in trough concentration with respect to its optimum level (< 5 mg/L) had been studied (Table 4). Preterm infants under 32 weeks of

Table 4: Study of variation and modified Amikacin peak and trough concentration at 3rd and 6th dose.

Patients	Pateint 1		Pateint 2		Pateint 3		Pateint 4		Pateint 5	
Doses No.	3rd	6th	3rd	6th	3rd	6th	3rd	6th	3rd	6th
# Changes in trough and peak concentration observed between 3 rd and 6 th dose.										
Changes of Trough	-0.25		+0.50		-7.49		-6.00		-6.00	
Changes of Peak	+1.14		+2.72		-5.62		+0.65		-3.00	
# Trough concentration study with respect to its optimum level (<5 mg/L)										
Deviation of Trough Conc.	-	-	-	-	+5.39	-2.1	+4.5	-1.5	+5	-1

# Amikacin Trough Concentration Study at 6 th Dose:			
Patients	Patient 3	Pateint 4	Pateint 5
Percentage of target Trough Conc. (%)	61.50	57.89	60.00
Percentage of achieved Trough Conc. (%)	72.09	63.16	60.00
Percentage Response (%)	117.21	109.09	100.00

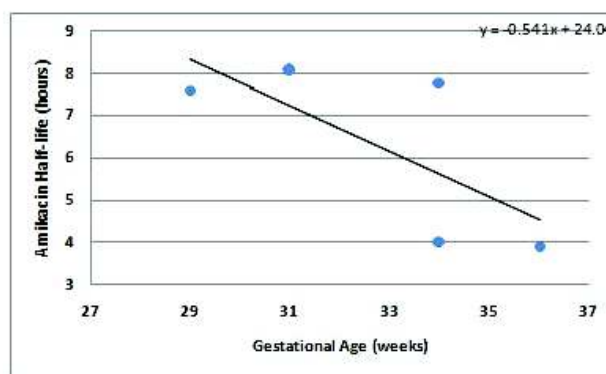
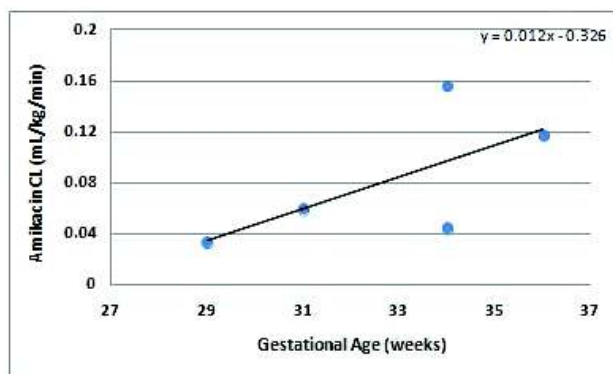


Figure 4: (a) Correlation between preterm infants gestational age and amikacin total body clearance.

Figure 4: (b) Inverse correlation between preterm infants gestational age (weeks) and amikacin half-life (hours).

gestational age showed high trough level. Modulated 6th dose results in trough values reaching an adequate level. Achievement in obtaining the optimal trough level from the inadequate level of 3rd to 6th dose was found 100% (Table 3).

Modification of dose and dosing time interval from 3rd to 6th dose had been studied (Table 3). Correlation study had been performed between the percentage modification of dose and dosing time interval with percentage changes of amikacin peak and trough concentration in all preterm infant patients at 6th dose (Figure 3). It shows that and patient 1 and 2, percentage modification of the dose and dosing time interval was at zero level. However, in other patients observed modification of dose ranged between 20% to 40% and dosing time interval between 60% to 80% with changes in peak and trough concentration.

The correlation between gestational age and total body clearance of amikacin was studied (Figure 4). It was found that total body clearance of amikacin varied directly with preterm infants gestational age and revealed a positive correlation ($y = 0.0125 \text{ PC Age} - 0.3269$; $r = 0.43$). The correlation between gestational age and amikacin half-life was found negative ($y = -0.5416 \text{ PC Age} + 24.047$; $r = 0.50$) (Figure 5). No correlation was observed between body weight and several dependent variables (gestational age, total body clearance).

Preterm infants and neonates remain one of the last therapeutic orphans to be adopted^[23,24]. FDA Safety and Innovation Act (FDASIA) functioning on neonatal pharmacotherapy improvisation has established a Neonatal Subcommittee of the Pediatric Advisory Committee to support neonatal

pharmacological research. Under the Federal Legislation (FDA, USA, 1997 - 2000) around 406 pediatrics drugs labeling have been changed but very few resulted in neonatal labeled indications. The federal US legislation and European Union legislation is attracting the attention on pediatric studies^[25,26].

CONCLUSION:

We concluded that preterm infant with gestational age of under 32 weeks required modulated amikacin dosage regimen even if serum creatinine level was found under normal range. Intensive monitoring of both peak and trough levels is recommended which helps in optimizing amikacin therapy by increasing its efficacy and minimizing toxicity in preterm infants. Percentage of modified dose and dosing time interval shows the percentage of inadequate trough concentration modified to obtain an optimized therapeutic level. Trough percentage response reflects the achievement in acquiring trough concentration in patients from targeted level, which was found $\leq 100\%$ result.

ACKNOWLEDGMENT:

The authors are grateful to Dr Alka D Kale and co-guide Dr Manisha Bhandankar for help and support. We would like to express our sincere appreciation towards Neonatal Intensive Care Unit at Karnataka Lingayat Education, Dr Prabhakar Kore Hospital & Medical Research Center for collaboration and providing clinical samples for study.

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Cite this article as: Chauhan B & Sunil J: Study of Preterm Infants with Different Gestational Age: Modifying Amikacin Sulphate Dosage Regimen . *PJSR* ;2017;10(2):8-16.
Source of Support : Nil, **Conflict of Interest:** None declared.